Inhibitory control for emotional and neutral scenes in competition: An eye-tracking study in bipolar disorder

Ana García-Blanco [1] [2], Ladislao Salmerón [3], and Manuel Perea [3] [4]

[1] Health Research Institute La Fe, Valencia, Spain

[2] Department of Personality, Evaluation, and Psychological Treatment, University of Valencia, Valencia, Spain

[3] ERI-Lectura, University of Valencia, Valencia, Spain

[4] Basque Center on Cognition, Brain, and Language, San Sebastián, Spain

Address for correspondence:

Ana C. García-Blanco

Health Research Institute La Fe

Av. Fernando Abril Martorell, 106

46010 Valencia (Spain)

Telephone: +34 961 245553

Email: ana.garcia-blanco@uv.es

Abstract

The present study examined the inhibitory control of attention to social scenes in manic, depressive, and euthymic episodes of Bipolar Disorder (BD). Two scenes were simultaneously presented (happy/threatening/neutral [target] vs. control). Participants were asked either to look at the emotional pictures (i.e., attend-to-emotional block) or to avoid looking at the emotional pictures (i.e., attend-to-neutral block) while their eye movements were recorded. The initial orienting (latency and percentage of first-fixation) and subsequent attentional engagement (gaze duration) were computed. Manic patients showed a higher percentage of initial fixations on happy scenes than on the other scenes regardless of the instructions. However, in the attend-to-neutral block, their gaze durations were longest for threatening scenes. Inhibitory control was not modulated by the scene's emotional salience in the other groups. Thus, manic patients had difficulties voluntarily ignoring emotional information—this was characterized by a happy-related bias during initial orienting, but a threat-related bias during attentional engagement.

Keywords: emotional processing; mood-congruent biases; attention; inhibitory control; bipolar disorder

Highlights

- We examined the inhibitory control of attention to emotional scenes in bipolar disorder

- Eye movements were registered to assess these processes

- Manic patients showed a happy-related bias during initial orienting

- Manic patients showed a threat-related bias during attentional engagement

- No biases were found for euthymic and depressed patients

Bipolar disorder (BD) is a mood disorder characterized by episodes of abnormal, persistent high mood (mania) and, at times, low mood (depression), together with remission episodes (euthymia) (Goodwin & Jamison, 2007). Whilst the last publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) includes mood dysregulation as a new clinical entity for BD, the underpinnings of how mood dysregulation occurs in BD is still under discussion (see Brotman et al., 2007).

To understand what emotion dysregulation entails in BD, it is fundamental to assess whether individuals are able to voluntarily control emotional responses in terms of directing attention to emotionally relevant stimuli (see Gratz & Roemer, 2004; Phillips et al., 2008). In the present experiment, we do so by simultaneously presenting two images (i.e., target [happy, threatening, or neutral] versus control [neutral]) to which BD patients in their different episodes (mania, depression, and euthymia) have to respond according to specific instructions (i.e., pay attention only to the emotional picture versus pay attention only to the neutral picture) while their eye movements are recorded—note that the recording of the participants' eye-movements is an excellent procedure to assess the temporal (duration) and spatial (location) measures of attentional capture (see Rayner, 2009, for a review on cognitive processes and eye movements).

Recent eye-tracking research in our lab has examined how the inhibitory control of attention is captured by emotional stimuli as a function of the BD patients' mood (e.g., García-Blanco, Perea, & Salmerón, 2013). Specifically, García-Blanco et al. (2013) conducted an emotional antisaccade experiment with happy, sad, and neutral faces in BD patients (during mania, depression, and euthymia episodes). A group of healthy individuals served as controls. Participants had to inhibit the automatic

prosaccade and voluntarily generate an antisaccade to the opposite location. Results showed that manic and depressed BD patients committed more antisaccade errors than control individuals—this difference was absent in euthymic BD patients. Importantly, manic BD patients committed more antisaccade errors with happy faces, whereas depressed BD patients showed a non-significant trend to commit more antisaccade errors with sad faces. Neither euthymic BD patients nor control individuals showed differences across conditions. García-Blanco et al. (2013) concluded that BD patients had an impaired ability to inhibit their attentional orienting toward mood-congruent stimuli during abnormal mood states, especially during manic episodes. This pattern provides some support to the Beck's Cognitive Model (1976) for BD: negative schemata would characterize depression and positive schemata would characterize mania.

Clearly, antisaccade tasks offer valuable information with respect to the initial orienting of attention. However, in addition to initial orienting, attentional capture involves other attentional processes such as the engagement of attention paid to a particular image when looking at it for the first time before looking away from it (see Posner & Petersen, 1990). Another potential limitation of the García-Blanco et al. (2013) experiment is that they only used happy and sad images as emotional stimuli. Freeman, Garety, Kuipers, Fowler, and Bebbington (2002) showed that BD patients have difficulties ignoring threatening stimuli. Indeed, threat-related schemata may underline psychotic states and paranoid traits in BD, especially during manic episodes (see Mansell, Morrison, Reid, Lowens, & Tai, 2007). To overcome these difficulties, García-Blanco et al. (2015) simultaneously displayed a target scene (happy, threatening, neutral) and a neutral control scene for 3 seconds in a free-viewing task with BD patients—a group of healthy individuals was included as a control. Participants' initial

orienting of gaze (i.e., the location of the first-fixation) was directed more frequently toward emotional images (both happy and threatening) than toward neutral images in all groups. However, unlike healthy individuals, BD patients (regardless of their episode) showed greater attentional engagement (i.e., sum of fixation durations before leaving the item [gaze duration]) to threatening scenes relative to neutral ones (see also García-Blanco, Salmerón, Perea, & Livianos, 2014, for similar evidence in a free viewing task with four simultaneously presented images). This threat-related bias is consistent with the idea that threat-related information is highly salient in BD (see Freeman et al., 2002). Importantly, these biases occurred during attentional engagement but not during initial orienting.

Of particular interest here is examining whether BD patients can modify their attentional biases and ignore distracting information that attracts attention. The idea is that a deficit to control attention that overrides voluntarily dominant responses may induce abnormal emotional reactions that entail difficulties in emotional self-regulation. However, free-viewing tasks such as the task used by García-Blanco et al. (2015) do not provide a measure of inhibitory control of attention per se. In the present experiment, we modified the instructions given in the García-Blanco et al. (2015) experiment so that we could directly obtain a direct measure of inhibitory control: in one block, participants were instructed to only attend to the emotional image, whereas in the other block participants were instructed to only attend to the neutral image (see Nummenmaa, Hyönä, & Calvo, 2006, for a similar procedure with healthy individuals). To be able to look at only one of the two images, participants need to: (i) recognize the correct scene by means of peripheral vision; (ii) fixate on this scene; and (iii) keep fixating on this scene until the completion of the trial. As healthy individuals in free-viewing tasks tend to orient their attention more frequently toward emotional images than neutral ones (see

Nummenmaa et al., 2006), the attend-to-neutral block involves a controlled inhibition: participants are required to inhibit the automatic response to emotional images and voluntarily direct their gaze to neutral pictures. With healthy individuals in the attend-to-neutral block, Nummenmaa et al. (2006) found that the percent of first fixations were higher and the gaze duration was longer for emotional than for neutral images—this pattern was not modulated by stimulus valence (happy versus threatening). That is, in attend-to-neutral blocks, healthy individuals have difficulty in ignoring emotional information in terms of both initial orienting (i.e., emotional images received a higher percent of first fixations than neutral images) and attentional engagement (i.e., emotional images received longer gaze durations than neutral images).

To sum up, the main goal of the present experiment was to examine inhibitory control across the three BD states (manic, euthymic, depressed) as a function of the type of target scene (happy, threatening, and neutral). The two main research questions were: (i) whether manic BD individuals would show higher deficit in inhibitory control for happy pictures than for neutral or threatening images (i.e., a mood-congruent bias), as Beck's (1976) theory would predict); or (ii) whether BD individuals—regardless of their episode—would show higher deficit in inhibitory control for threatening images than for happy and neutral ones (i.e., a bias toward threatening information), as Freeman et al.'s (2002) cognitive model would predict). To shed some light on these two questions, we examined two attentional components (see also Nummenmaa et al., 2006, for a similar approach): 1) initial orienting of attentional capture (i.e., the latency of the first fixation and the percentage of the first fixation); and 2) attentional engagement (i.e., the gaze duration).

Method

Participants. Eighty-four BD patients from the Psychiatry Department at the "La Fe"

University and Polytechnic Hospital (Valencia, Spain) and 27 healthy individuals recruited through advertising in the community took part in the experiment. Patients fulfilled the DSM-IV-TR criteria for BD and were included in the manic (n = 29), depressed (n = 27), or euthymic (n = 28) group at the time of assessment. BD patients were recruited from inpatient wards (n = 40) and from Bipolar Disorders Unit for outpatients (n = 44). Four patients in manic episodes refused to cooperate. The ethics committee of the "La Fe" Health Research Institute authorized this study. Demographic and clinical details are presented in Table 1.

Table 1. Demographic and clinical data from control group, depressed, euthymic and manic patients. Data shown are averages and standard deviations.

	Control	Euthymic	Depressed	Manic	p
	(N = 27)	(N = 28)	(N = 27)	(N = 29)	
% Female	48.1	39.3	44.4	44.8 .93	
Age	42.0 (12.6)	41.1 (10.3)	49.4 (9.8)	44.4 (12.0)	.05
SASS	43.8 (6.0)	40.1 (5.3)	40.8 (6.8)	39.5 (6.2)	.07
# of episodes	-	6.1 (5.3)	7.6 (4.5)	7.1 (5.6)	.56
BAI	11.2 (7.0)	6.3 (5.0)	24.9 (90)	11.5 (7.3)	**.000**
BDI	5.9 (6.0)	3.4 (41)	25.8 (7.9)	5.1 (3.6)	**.000**
YMRS	-	1.2 (2.2)	1.8 (2.4)	23.7 (5.5)	**.000**
Medication (% of patients)					
Lithium (%)	-	89.3	70.4	72.4	.18
Antiepileptic (%)	-	46.4	66.7	41.4	.14
Antipsychotic (%)	-	39.3	48.1	96.6 **.000**	

Antidepressive (%)	-	7.1	55.6	6.9	**.000**
Anxiolytic (%)	-	42.9	81.5	89.7	**.000**

Note: the p values correspond to the omnibus test for all groups

No participant showed difficulty in obtaining stable eye tracking (e.g., eye diseases, interference from glasses, or frequent crying) or major medical disorders, neurological history, or use of non-psychotropic medication that could influence cognition (e.g., treatment with corticosteroids). No healthy control reported any kind of psychiatric history. Additional exclusion criteria for patients were i) other psychiatric diagnoses based on the DSM-IV-TR criteria (American Psychiatric Association [APA], 2000) and ii) having received electroconvulsive therapy within the previous 3 months. All patients were referred by psychiatrists in the Bipolar Disorders Unit who diagnosed the BD patients following the DSM-IV-TR criteria. The responsible psychiatrist together with a postgraduate clinical psychology intern corroborated the BD diagnosis via a clinical interview and case note review. Every BD patient had to present at least one manic episode. The Young mania rating scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) were used to control the presence of affective symptoms in healthy participants and in euthymic patients and to exclude mixed states (BDI-II scores < 9, except in the depressed group > 18; YMRS scores < 6, except in the manic group > 20). Additionally, every participant filled out: i) the Social Adaptation Self-Evaluation Scale (SASS; Bosc, Dubini, & Polin, 1997) to assess social functioning; and ii) the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) to measure anxiety. Six of the 117 participants in the original sample (89 patients, 28 healthy controls) were excluded based on these criteria, resulting in a final sample of 111 participants.

Apparatus. The participants' eye movements were monitored using a remote eye tracking system (SMI RED250). This system allows the participant free head movements across a wide range. The sampling rate of gaze-point position was 250 Hz. Areas of interest (AOIs) were also identified for each trial and corresponded to the total area for each of the target images.

Materials. We used the same images employed by Nummenmaa et al. (2006) in their Experiment 2. The stimuli were 128 pictures taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005). A total of 16 happy and 16 threatening target scenes together with 16 neutral scenes and 80 control images were employed. The control pictures illustrated various inanimate images and non-living objects, whereas the neutral images represented animate scenes with people in non-emotional activities or aspects of daily life. The happy target scenes represented people showing positive affect or taking pleasure in something. The threatening target scenes depicted aggressive people or people suffering from serious threat or harm.

In each trial, two pictures appeared, namely a target scene (happy, threatening, or neutral) and a control picture, where the emotional scene and control images were randomly paired. Each trial began with a centrally presented fixation cross located in the middle of the screen, followed by simultaneous presentation of two images for 3,000 ms. There were three types of experimental trials—16 happy-control, 16 threatening-control, and 16 neutral-control. In addition, 16 pairs of control-control trials were used as filler trials to mask the nature of the task. Each trial was displayed two times. Overall, the experimental session comprised a total of 128 trials (96 experimental + 32 filler). For each trial, the images were displayed in two opposing corners of the screen (top right/bottom left or top left/bottom right). The horizontal and vertical locations of the target pictures were balanced across trials, keeping in mind that each stimulus

category had to appear in each of the four positions four times across 16 trials. The presentation order of the scenes was randomized across participants. The participants were not able to use any predetermined scanning strategy due to the variation in the picture positions and the randomization of trials (see Fig. 1).

Fig. 1. Stimulus sequence of two experimental trials with a threatening and happy target scene.

Procedure. After signing an informed consent form, all participants completed a demographic interview and the SSAS, BAI and BDI rating scales. Additionally, patients completed a clinical interview and the YMRS. In the same session, participants carried out the experiment in a dimly lit room. They were tested individually and were seated in a height adjustable chair approximately 60 cm from the screen. The experimental session began once the eye-tracker was successfully calibrated (i.e. average error was

less than 1.5° of visual angle for each calibration point) and six practice trials were completed.

The 128 trials were divided into two blocks. Each participant performed the task with both blocks, which were counterbalanced across participants. Before each block, the participant was instructed to either i) "direct your gaze to an emotional image and keep it there as long as the images are presented" (attend-to-emotional block), or ii) "direct your gaze to a neutral image and keep it there as long as the images are presented" (attend-to-neutral block). Each stimulus pair appeared only once in the attend-to emotional and once in the attend-to-neutral condition.

Data analyses. We measured the following eye-movement measures: (a) the latency of the first fixation (i.e., the time taken to fixate on a target picture); (b) the percentage of first fixations (i.e. the percentage of trials in which the first fixation was on a target picture); (c) the gaze duration (i.e. the sum of fixation durations on a target picture when it is looked at for the first time and before leaving it); and (d) the total fixation time (i.e. the overall gaze duration with possible re-fixations on a target picture during the 3-sec exposure period). Initial orienting was assessed through the latency of the first fixation and the percentage of first fixation on a target picture. The gaze duration assessed subsequent attentional engagement. Finally, the total fixation time assessed allocation of attention—this measure was included in order to verify that the participants followed the instructions appropriately for each block.

Results

The descriptive statistics (means and standard errors) on the eye movement measures for the different target types are displayed in Table 2. Eye movement measures were analyzed in a 4 (Group: control, euthymic, depressed, manic) x 3 (Valence of image:

happy, threatening, neutral) x 2 (Block: attend to neutral, attend to emotional) analysis of variance (ANOVA) in which Group was a between-subjects factor and Valence and Block were within-subject factors. In the case of significant interactions, Bonferroni corrections were employed in the simple effect tests.

<u>Initial orienting</u>

Latencies of the first fixation. The ANOVA showed a main effect of Group, $F(3,107) = 9.59$, $p < .001$, $\eta^2 = .21$: on average, latencies of the first fixation were longer in the manic (708 ms) and depressed (717 ms) groups than in the control (556 ms) and euthymic (575 ms) groups (all $ps < .005$). The main effects of Block, $F(1,107) = 11.34$, $p = .001$, $\eta^2 = .10$, and Valence, $F(2,107) = 11.34$, $p < .001$, $\eta^2 = .10$ were also significant. Only the Block x Valence interaction was significant, $F(2, 107) = 3.18$, $p = .043$, $\eta^2 = .03$—all other interactions had $ps > .41$.

To analyze the Block x Valence interaction, we tested the effect of Valence in each Block. We found an effect of Valence in the attend-to-neutral block, $F(2, 220) = 11.50$, $p < .001$, $\eta^2 = .10$, but not in the attend-to-emotional block, $F(2, 220) = 1.95$, $p = .14$. Further analyses on the attend-to-neutral block showed that latencies were shorter for happy pictures (617 ms) than for neutral (717 ms) and threatening (665 ms) pictures (both $ps < .04$)—these two conditions did not differ significantly ($p = .07$).

Percentage of the first fixations. The ANOVA showed a main effect of Block, $F(1, 107) = 61.38$, $p < .001$, $\eta^2 = .37$, Valence, $F(2, 214) = 10.39$, $p < .001$, $\eta^2 = .09$, and Group, $F(3, 107) = 2.98$, $p = .03$, $\eta^2 = .08$. Importantly, the Group x Valence interaction, $F(6,107) = 4.03$, $p = .001$, $\eta^2 = .10$, and the Group x Block interaction, $F(3,107) = 7.48$,

$p < .001$, $\eta^2 = .17$ were significant. The other interactions were not significant, all Fs < 1.

To analyze the Group x Valence interaction, we examined the effect of Valence in each group (see Fig. 2). The effect of Valence was significant in the control ($F(2, 52) = 10.96$, $p < .001$, $\eta^2 = .30$), euthymic ($F(2, 54) = 3.33$, $p = .043$, $\eta^2 = .11$) and manic ($F(2, 56) = 12.22$, $p < .001$, $\eta^2 = .30$) groups, but not in the depressed group ($F < 1$). For the control group, threatening images received a higher percentage of initial fixations than neutral images (69.91% vs. 58.50%, respectively) ($p < .001$), and none of them differ significantly from the happy images (65.89%) (all ps > .06). For the euthymic group, even though the main effect was significant, there were no significant differences across levels of Valence (happy: 56.09%, threatening: 64.36%, neutral: 59.00%; all ps > .10). For the manic group, happy images received a higher percentage of initial fixations (65.15%) than threatening (59.05%) and neutral images (53.05%) (both ps < .03)—these two condition did not differ significantly ($p = .09$).
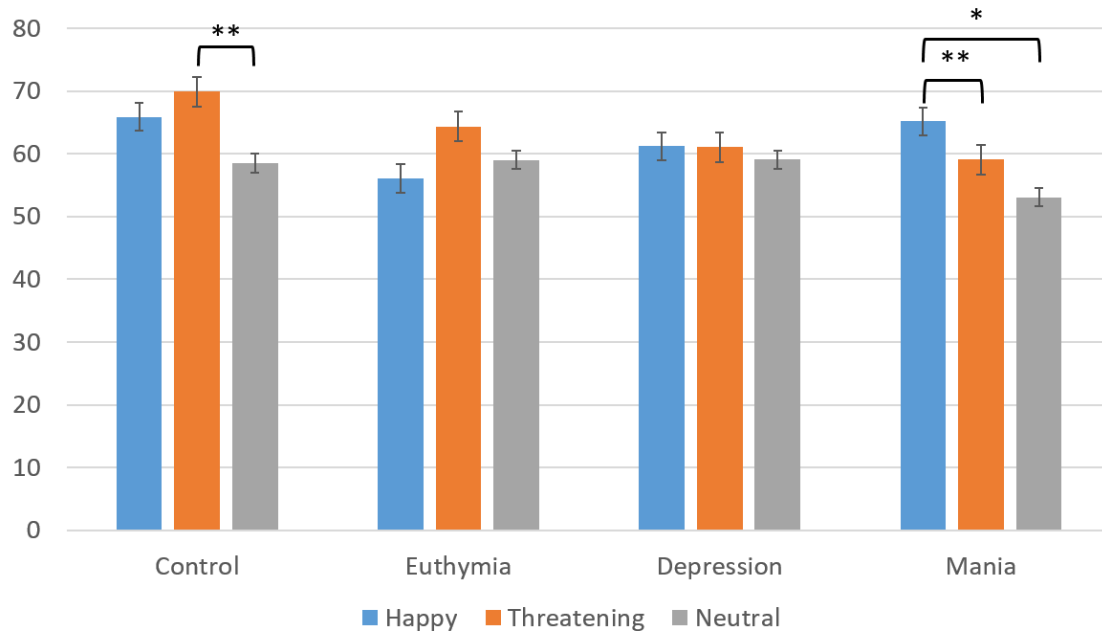

Fig. 2. Percentage of initial fixation (%) for valence and group. Data shown are means and standard errors.

To analyze the Group x Block interaction, the effect of Block was examined for each group. The effect of Block was significant in the control ($F(1, 26) = 31.80$, $p < .001$, $\eta^2 = .55$), euthymic $(F(1, 27) = 13.88$, $p = .001$, $\eta^2 = .34)$ and manic ($F(1, 28) = 15.25$, $p = .001$, $\eta^2 = .35$) groups, but not in the depressed group, $F(1, 26) = 2.76$, $p = .11$. The percentage of initial fixations on the target picture was higher in the attend-to-emotional blocks (control: 76.29%, euthymic: 65.18%, manic: 63.33%) than in the attend-to-neutral blocks (control: 53.24%, euthymic: 65.18%, manic: 63.33%) in all groups except for the depressed group (attend-to-emotional: 62.37%, attend-to-neutral: 58.42%).

Attentional engagement

Gaze duration. The ANOVA revealed significant main effects of Block ($F(1,107) = 427.22$, $p < .001$, $\eta^2 = .80$), Valence ($F(2,214) = 7.76$, $p < .001$, $\eta^2 = .07$), but not of Group ($F(1,107) = 1.26$, $p < .29$). Importantly, these effects were qualified by the Block x Valencia x Group interaction ($F(6,214) = 2.47$, $p = .025$, $\eta^2 = .06$). To analyze this three-way interaction, we examined the Valence x Group interaction in each level of the factor Block (see Fig. 3).
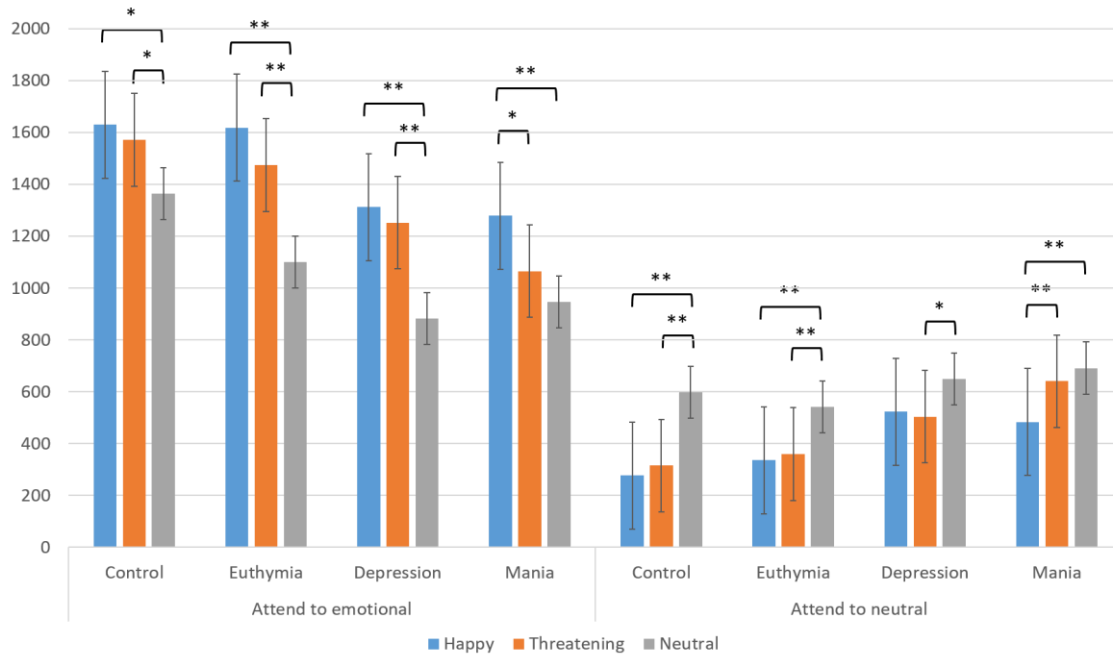
Fig. 3. Gaze duration (ms) for block, valence, and group. Data shown are means and standard errors.

In the attend-to-emotional block, the main effects of Valence ($F(2, 214) = 60.41$, $p < .001$, $\eta^2 = .36$) and Group ($F(3, 107) = 7.32$, $p < .001$, $\eta^2 = .17$) were qualified by a significant Valence x Group interaction ($F(6, 214) = 2.16$, $p = .048$, $\eta^2 = .06$). To examine this interaction, the effect of Valence was analyzed in each group. The effect of Valence was significant in all groups (control: $F(2, 52) = 5.68$, $p = .006$, $\eta^2 = .18$; euthymic: $F(2, 54) = 29.52$, $p < .001$, $\eta^2 = .52$; manic: $F(2, 56) = 10.60$, $p < .001$, $\eta^2 = .28$; depressed: $F(2, 52) = 29.86$, $p < .001$, $\eta^2 = .53$). As shown in Table 2, the pattern of data was similar in the control, euthymic, and depressed groups: gaze durations were shorter on neutral targets than on happy and threatening targets (all ps $< .02$)—there were no significant differences between these two conditions (all ps $> .13$). In contrast, manic patients showed a different pattern: gaze durations were longer on happy targets than on threatening or neutral targets (both ps $< .01$)—there were no significant differences between these two conditions ($p = .25$).

Table 2. Mean (standard deviation) for the latency of first fixation, the percentage of first fixation, the gaze duration, and the total fixation duration for each stimulus category for the control (C), euthymic (E), depressed (D) and manic (M) groups

Stimulus category		Latency of first fixation (ms)				Percent first fixation (%)				Gaze duration (ms)				Total fixation duration (ms)			
		C	E	D	M	C	E	D	M	C	E	D	M	C	E	D	M
Emotional	Happy	518 (168)	553 (144)	681 (224)	657 (209)	80.4 (18.4)	61.6 (19.5)	62.4 (16.6)	69.0 (18.2)	1629 (520)	1618 (460)	1312 (428)	1278 (452)	1703 (521)	1835 (367)	1397 (488)	1451 (444)
	Threatening	549 (195)	513 (107)	686 (209)	665 (173)	80.5 (14.8)	70.5 (18.7)	64.4 (16.8)	64.7 (15.7)	1571 (552)	1474 (341)	1252 (373)	1065 (394)	1721 (546)	1774 (292)	1387 (442)	1286 (380)
	Neutral	575 (205)	570 (120)	681 (265)	706 (154)	67.9 (9.1)	63.4 (14.4)	60.3 (13.5)	56.4 (14.0)	1364 (607)	1100 (467)	883 (370)	945 (366)	1575 (535)	1471 (419)	1127 (461)	1092 (339)
Neutral	Happy	541 (156)	563 (161)	693 (309)	670 (197)	51.4 (22.3)	50.6 (19.2)	59.8 (20.0)	61.3 (16.3)	276 (228)	335 (140)	522 (281)	483 (280)	231 (211)	282 (161)	519 (315)	488 (325)
	Threatening	561 (195)	619 (184)	731 (287)	746 (177)	59.3 (19.8)	58.2 (16.3)	57.6 (16.2)	53.4 (14.9)	315 (181)	359 (148)	504 (230)	640 (275)	283 (236)	328 (179)	494 (288)	664 (349)
	Neutral	593 (144)	633 (193)	832 (376)	807 (177)	49.1 (15.1)	54.6 (17.4)	57.8 (11.3)	49.7 (12.4)	597 (338)	541 (278)	649 (333)	691 (279)	588 (311)	569 (306)	721 (328)	725 (292)

In the attend-to-neutral bock, the main effects of Valence ($F(2, 214) = 37.87$, $p < .001$, $\eta^2 = .26$) and Group ($F(3, 107) = 7.38$, $p < .001$, $\eta^2 = .17$) were also qualified by a significant Valence x Group interaction ($F(6, 214) = 2.66$, $p = .02$, $\eta^2 = .07$). To analyze this interaction, we examined the effect of Valence in each group. The effect of Valence was significant in all groups (control: $F(2, 52) = 18.46$, $p < .001$, $\eta^2 = .42$; euthymic: $F(2, 54) = 10.82$, $p < .001$, $\eta^2 = .29$; manic: $F(2, 56) = 8.46$, $p < .001$, $\eta^2 = .23$; depressed: $F(2, 52) = 5.67$, $p = .006$, $\eta^2 = .18$). There was a common pattern in the control, euthymic, and depressed groups: gaze durations were longer on neutral targets than on happy or threatening targets (both ps $< .05$)—there was no significant difference between happy and threatening pictures ($p > .90$). Again, manic patients showed a different pattern: gaze durations were longer on threatening and neutral images than on happy pictures (both ps $< .003$), whereas there was no significant difference between threatening and neutral pictures ($p > .90$).

Overall allocation of attention

Total fixation time. The ANOVA of the total fixation time showed a significant main effect of Block ($F(1,107) = 708.76$, $p < .001$, $\eta^2 = .87$), but not of Valence or Group (both $Fs < 1$). Importantly, these effects were qualified by a significant Valence x Group x Instruction interaction ($F(6, 214) = 2.31$, $p = .03$, $\eta^2 = .06$). To further analyze this interaction, we tested the Valence x Group interaction in each Block.

In the attend-to-emotional block, we found main effects of Valence ($F(2, 214) = 46.77$, $p < .001$, $\eta^2 = .30$) and Group ($F(3, 107) = 8.88$, $p < .001$, $\eta^2 = .20$). The Valence x Group interaction did not reach statistical significance ($F(6, 214) = 2.04$, $p = .06$, $\eta^2 = .05$). With respect to the effect of Valence, total fixation times were shorter on

neutral targets that on happy and threatening targets (both ps < .001)—there was no significant difference between these two conditions ($p = .24$). With respect to the effect of Group, total fixation times were similar in the control and euthymic groups ($p > .90$), which in turn were longer than those in the manic and depressed groups (all $ps < .001$). Finally, the total fixation times were similar in the manic and depressed groups ($p > .90$).

In the attend-to-neutral block, the main effects of Valence ($F(2, 214) = 56.84$, $p < .001$, $\eta^2 = .35$) and Group ($F(3, 107) = 8.74$, $p < .001$, $\eta^2 = .20$) were qualified by a significant interaction between these two factors ($F(6, 214) = 2.70$, $p = .01$, $\eta^2 = .07$). To analyze this interaction, the effect of Valence was examined in each group. The effect of Valence was significant in all groups (control: $F(2, 52) = 22.00$, $p < .001$, $\eta^2 = .46$; euthymic: $F(2, 54) = 26.14$, $p < .001$, $\eta^2 = .49$; manic: $F(2, 56) = 11.45$, $p < .001$, $\eta^2 = .29$; depressed $F(2, 52) = 8.93$, $p < .001$, $\eta^2 = .26$). We found a similar pattern in the control, euthymic and depressed groups: total fixation durations were longer on neutral images than on happy and threatening images (all $ps < .001$)—these two conditions did not differ significantly ($p > .31$). In contrast, for manic patients, total fixation durations were longer on threatening and neutral images than on happy images (all $ps < .002$)— total fixation times on threatening and neutral pictures did not differ significantly ($p = .99$).

Discussion

The present eye-movement experiment was designed to examine how the emotional valence of images (happy, threatening, and neutral) affects the inhibitory control of attentional capture (initial orienting and attentional engagement) in the different episodes of BD patients (mania, euthymia, and depression). First, we had initially

hypothesized—following Beck's (1976) theory, that manic BD individuals would show a deficit in inhibitory control for happy pictures. In the initial orienting, we found that manic BD patients showed a higher percentage of initial fixations on happy scenes than on the other scenes regardless of the instructions. Second, we had hypothesized—in terms of Freeman's et al. (2002) theory—that BD patients (regardless of their episode) would show difficulties ignoring threatening stimuli. Our findings on attentional engagement partially support this hypothesis, but it was restricted to manic BD patients: In the attend-to-neutral block, manic BD patients had longer gaze duration for threatening and neutral scenes than for happy scenes. Therefore, manic patients show a deficit in inhibitory control for happy scenes in initial orienting, whereas they show a deficit in inhibitory control for threatening scenes in attentional engagement. In the following paragraphs, we discuss the implication of these findings for Beck's (1976) cognitive theory on mania and Freeman et al.'s (2002) cognitive model.

Regarding the inhibitory control of initial orienting to emotional stimuli, manic and depressive individuals showed slower latencies of the first fixation than euthymic and control individuals. In addition, when the percentage of the first fixation was analyzed, manic BD patients showed an initial orienting bias toward happy scenes regardless of the instructions. This pattern resembles that found in the García-Blanco et al. (2013) experiment with manic patients in which there were more antisaccade errors (i.e., a deficit to inhibit an automatic prosaccade) to happy stimuli than to sad or neutral faces. The happy-related bias during initial orienting in manic BD patients is consistent with Beck's Cognitive theory on mania (1976): mania involves positive biases in information processing. In the present experiment, the stimulus valence modulation of initial orienting was absent in depressed BD patients (see García-Blanco et al., 2013, for a similar finding with an antisaccade task). Thus, depressive BD patients showed an

"anhedonic bias" rather than a negative bias as Beck's cognitive theory (1976) postulates. The lack of emotional bias in bipolar depression may be explained by the distinctive feature of BD relative to major depressive disorder (Mansell et al., 2007) because melancholic symptoms (e.g., loss of pleasure in activities or lack of reactivity to emotional stimuli) are more characteristic of bipolar than unipolar depression. Finally, healthy participants showed a threat-related bias during initial orienting, regardless of the instructions. As indicated earlier, previous eye-tracking studies reported preferential initial orienting towards threatening scenes (Santos et al., 2012). This bias has been interpreted as an adaptive threat-detection advantage that may represent an evolutionary advantage for survival (see Öhman, 2009). Therefore, vigilance concerning threatening stimuli, despite the instructions to ignore them, may be a survival function that is conserved in healthy individuals.

With respect to the inhibitory control of attentional engagement, we found that gaze durations were longer on neutral than on emotional images in all groups, except in the manic group. Specifically, manic BD patients showed longer gaze durations on threatening and neutral scenes than on happy scenes. That is, manic BD patients showed a threat-related bias. This finding is consistent with theoretical proposals that emphasize the relevance of threat-related schemata in BD (Freeman et al., 2002). Importantly, unlike free-viewing tasks (García-Blanco et al., 2014; García-Blanco et al., 2015), this threat-related bias did not occur in depressed or euthymic BD patients. That is, depressed and euthymic BD patients can inhibit the attentional engagement to threatening scenes and voluntarily direct their gaze to neutral pictures. This finding suggests that threatening scenes are especially salient in manic states. One explanation for this pattern is that threat-related schemata are more prominent during mania than other mood episodes (see Mansell et al., 2007). Indeed, we found that severity of manic

symptomatology had a modulating role in threat-related bias formation (Footnote 1). Taken together, the present data suggest a dissociation between initial orienting and attentional engagement in mania when the participant's task is to attend to neutral information: whereas manic BD patients are initially oriented to positive information, subsequently their attention is engaged in threat-related information. This difficulty to disengage attention from threatening images may contribute to threat-related rumination (Koster et al., 2011). Therefore, the impairment for inhibiting the automatic initial orienting of attention toward happy stimuli and the impairment for disengaging attention from threatening stimuli could be a key component of emotion dysregulation observed in mania (Alloy et al., 2006).

The current experiment also examined the blocks in which participants were instructed to attend to emotional information. Except for the individuals in the manic group, who showed the highest attentional capture for happy images, the other groups showed an attentional capture for emotional stimuli (both happy and threatening scenes received a higher percentage of first fixation than neutral images) (see García-Blanco et al., 2013; García-Blanco et al., 2015, for similar findings with a prosaccade task and a free-viewing task, respectively). Therefore, all groups of participants were able to recognize which was the correct target scene during early stages of processing—note that—while non-significant—the attentional capture of manic patients was higher for threatening than for neutral images.

Finally, the current eye-tracking experiment comes with certain limitations that are typical in studies with patients. All patients were medicated at the time of testing (see Table 1). We acknowledge that medication and other illness variables (i.e., number of previous episodes, age of illness onset) can affect inhibitory control. However, medication or historical illness variables alone cannot explain why attentional capture in

each episode was modulated by the emotional salience of stimuli. Nevertheless, manic and depressed individuals had slower latencies of the first fixations than euthymic and control individuals. We conducted post hoc analyses of covariance (ANCOVAs) that included antipsychotic, antidepressive, and anxiolytic medication as covariates. No medication significantly interacted with any of the main effects or interactions in the analyses (ps > .18 and ps > .09, respectively). Thus, medication was not the main cause of the differences across groups in the latencies of the first fixations.

In summary, the current eye-movement experiment adds to previous studies in BD that a manic state posits difficulties in inhibiting happy information during initial orienting and in inhibiting threatening information during attentional engagement. Therefore, despite the fact that threatening information is salient for all BD mood episodes when it is free-viewed, only manic patients had difficulties ignoring it voluntarily. Thus, our findings revealed an impaired inhibitory control in mania, which was modulated both by stimulus valence (happy vs. threatening) and by the component of attentional capture (initial orienting vs. attentional engagement). That is, inhibitory control when processing emotional information is impaired in BD, and this is especially so during manic episodes. This impairment may play an important role in an individual's emotion regulation. Indeed, a potential line of research at the applied level is the examination of whether attention training with emotional stimuli is a useful treatment target for BD individuals (see Wells & Beevers, 2010, for evidence with major depression).

Acknowledgements

Conflict of Interest

The authors declare that they have no conflict of interest.

References

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., & Neeren, A. M. (2006). Cognitive vulnerability to unipolar and bipolar mood disorders. *Journal of Social and Clinical Psychology, 25*, 726-754. doi:10.1521/jscp.2006.25.7.726

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders (text revision).* Washington, DC: Author.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (DSM-5). Arlington: American Psychiatric Publishing.

Beck, A.T. (1976). *Cognitive therapy and the emotional disorders.* New York: New American Library.

Beck, A.T., Epstein, N., Brown, G., & Steer R.A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology, 56,* 893–897. doi:10.1037/0022-006X.56.6.893

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory—II.* Psychological Corporation, San Antonio, TX.

Bosc, M., Dubini, A., & Polin, V. (1997). Development and validation of a social functioning scale, the Social Adaptation Self-Evaluation Scale. *European Neuropsychopharmacology, 7*, S57-S70. doi:10.1016/S0924-977X(97)00420-3

Brotman, M. A., Kassem, L., Reising, M. M., Guyer, A. E., Dickstein, D. P., Rich, B. A., Towbin, K. E., Pine, D. S., McMahon, F. J., & Leibenluft, E. (2007). Parental diagnoses in youth with narrow phenotype bipolar disorder or severe

mood dysregulation. *The American Journal of Psychiatry, 164*, 1238-1241. doi:10.1176/appi.ajp.2007.06101619

Freeman, D., Garety, P. A., Kuipers, E., Fowler, D., & Bebbington, P. E. (2002). A cognitive model of persecutory delusions. *British Journal of Clinical Psychology, 41*, 331-347. doi:10.1348/014466502760387461

García-Blanco, A. C., Perea, M., & Salmerón, L. (2013). Attention orienting and inhibitory control across the different mood states in bipolar disorder: An emotional antisaccade task. *Biological Psychology, 94,* 556-561. doi:10.1016/j.biopsycho.2013.10.005

García-Blanco, A., Salmerón, L., & Perea, M. (2015). Attentional capture by emotional scenes across episodes in bipolar disorder: Evidence from a free-viewing task. *Biological Psychology, 108,* 36-42. doi:10.1016/j.biopsycho.2015.03.010

García-Blanco, A. C., Salmerón, L., Perea, M., & Livianos, L. (2014). Attentional biases toward emotional images in the different episodes of bipolar disorder: An eye-tracking study. *Psychiatry Research, 215,* 628-633. doi:10.1016/j.psychres.2013.12.039

Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology and Behavioral Assessment, 26*, 41-54. doi:10.1023/B:JOBA.0000007455.08539.94

Goodwin, F. K., & Jamison, K. R. (2007). *Manic-depressive illness: bipolar disorders and recurrent depression.* Oxford University Press.

Santos, A., Chaminade, T., Da Fonseca, D., Silva, C., Rosset, D., & Deruelle, C. (2012).
Just another social scene: evidence for decreased attention to negative social
scenes in high-functioning autism. *Journal of Autism and Developmental
Disorders, 42,* 1790-1798. doi:10.1007/s10803-011-1415-6

Koster, E. H., De Lissnyder, E., Derakshan, N., & De Raedt, R. (2011). Understanding
depressive rumination from a cognitive science perspective: The impaired
disengagement hypothesis. *Clinical Psychology Review, 31,* 138–145.
doi:10.1016/j.cpr.2010.08.005

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). *International affective picture
system (IAPS): Affective ratings of pictures and instruction manual.* In Technical
Report A-6. Gainesville, FL: University of Florida.

Mansell, W., Morrison, A. P., Reid, G., Lowens, I., & Tai, S. (2007). The interpretation
of, and responses to, changes in internal states: An integrative cognitive model
of mood swings and bipolar disorders. *Behavioural and Cognitive
Psychotherapy*, *35,* 515-539. doi:10.1017/S1352465807003827

Nummenmaa, L., Hyönä, J., & Calvo, M. G. (2006). Eye movement assessment of
selective attentional capture by emotional pictures. *Emotion, 6,* 257–268.
doi:10.1037/1528-3542.6.2.257

Öhman, A. (2009). Of snakes and faces: An evolutionary perspective on the psychology
of fear. *Scandinavian Journal of Psychology*, *50,* 543-552. doi:10.1111/j.1467-
9450.2009.00784.x

Phillips, M.L., Ladouceur, C.D., & Drevets, W.C. (2008). A neural model of voluntary
and automatic emotion regulation: implications for understanding the

pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry*, *13*, 833-857. doi:10.1038/mp.2008.82

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25–42. doi:10.1146/annurev.ne.13.030190.000325

Rayner, K. (2009). Eye movements and attention in reading, scene perception, and visual search. *Quarterly Journal of Experimental Psychology*, *62,* 1457-1506. doi:10.1080/17470210902816461

Wells, T. T., & Beevers, C. G. (2010). Biased attention and dysphoria: Manipulating selective attention reduces subsequent depressive symptoms. *Cognition & Emotion, 24,* 719-728. doi:10.1080/02699930802652388

Young, R.C., Biggs, J.T., Ziegler, V.E., & Meyer, D.A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal Psychiatry*, *133*, 429-435. doi:10.1192/bjp.133.5.429

Footnotes

1. We computed the Pearson's coefficient to examine the relationship between attentional engagement to threat-related information (i.e., the gaze duration for threatening scenes) during the attend-to-neutral block and the YMRS scores (i.e. manic symptoms) in BD patients. YMRS scores were significantly correlated with the gaze duration for threatening scenes ($r = .418$, $p < .001$). That is, the higher the manic symptomatology, the higher attentional engagement to threatening scenes.